We claim:

1. A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1, which inhibitor(s) are administered in an amount sufficient to inhibit the dipeptidylpeptidase proteolysis of GLP-1.

2. A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis with a Ki of 1nM or less.

3. A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) and accordingly increase the plasma half-life of GLP-1.

4. A method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors dipeptidylpeptidase IV (DPIV).

5. The method of claim 1, wherein dipeptidylpeptidase is DPIV.

6. The method of claim 3, wherein protease inhibitor is an inhibitor of DPIV.

7. The method of claim 2 or 3, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia.

8. The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC50 for modification of glucose metabolism which is at least one order of magnitude less than its EC50 for immunosuppression.

9. The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC50 for inhibition of glucose tolerance in the nanomolar or less range

10. The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC50 for immunosuppression in the μM or greater range.

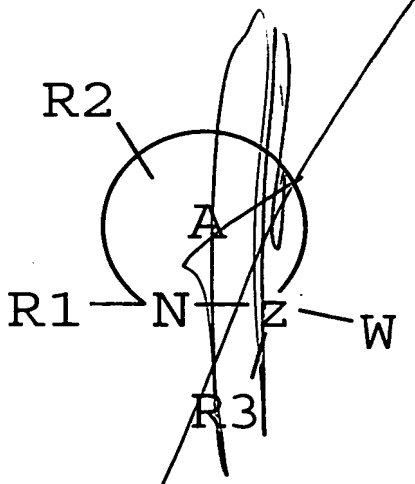
11. The method of claim 4, 5 or 6, wherein the inhibitor has a Ki for DPIV inhibition of 1.0 nm or less.

12. The method of claim 1, 2, 3 or 4, wherein the inhibitor is peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

13. The method of claim 1, 2, 3 or 4, wherein the inhibitor has a molecular weights less than 7500 amu.

14. The method of claim 1, 2, 3 or 4, wherein the inhibitor is orally active.

15 The method of claim 1, 2, 3 or 4, wherein the inhibitor is represented by the general formula;



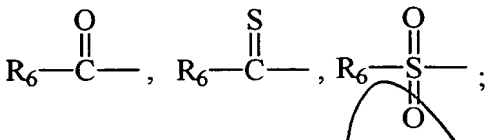

wherein

A represents a 4-8 membered heterocycle including the N and the Cα carbon;

Z represents C or N;

W represents a functional group which reacts with an active site residue of the targeted protease,

$R_1$ represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



$R_2$ is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_7$;

if X is N, $R_3$ represents hydrogen, if X is C, $R_3$ represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_7$;

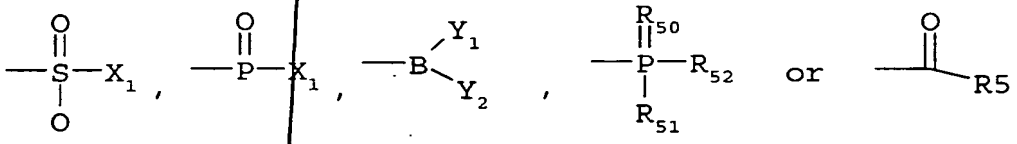
$R_6$ represents hydrogen, a halogen, a alkyl, a alkenyl, a alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, $-(CH_2)_m-S-(CH_2)_m-R_7$,

$R_7$ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

16. The method of claim 15, wherein

W represents -CN, $-CH=NR_5$,



$R_5$ represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)m-R_7$, $-(CH_2)n-OH$, $-(CH_2)n-O-alkyl$, $-(CH_2)n-O-alkenyl$, $-(CH_2)n-O-alkynyl$, $-(CH_2)n-O-(CH_2)m-R_7$, $-(CH_2)n-SH$, $-(CH_2)n-S-alkyl$, $-(CH_2)n-S-alkenyl$, $-(CH_2)n-S-alkynyl$, $-(CH_2)n-S-(CH_2)m-R_7$, $-C(O)C(O)NH_2$, $-C(O)C(O)OR'_7$;

$R'_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; and

$Y_1$ and $Y_2$ can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where $Y_1$ and $Y_2$ are connected via a ring having from 5 to 8 atoms in the ring structure (such as pinacol or the like),

$R_{50}$ represents O or S;

$R_{51}$ represents $N_3$, $SH_2$, $NH_2$, $NO_2$ or $OR'_7$;

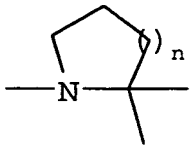
$R_{52}$ represents hydrogen, a lower alkyl, an amine, $OR'_7$, or a pharmaceutically acceptable salt, or $R_{51}$ and $R_{52}$ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure

$X_1$ represents a halogen;

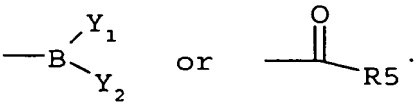
$X_2$ and $X_3$ each represent a hydrogen or a halogen

R1.126

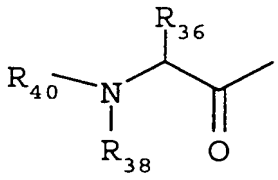
R.126 ~~18.~~ 17. The method of claim 16, wherein the ring A is represented by the formula



wherein n is an integer of 1 or 2.

R.126 R1.126 ~~19.~~ 18. The method of claim 16, wherein W represents  .

~~20~~ 19. The method of claim 16, wherein R1 represents



wherein

R36 is a small hydrophobic group and R38 is hydrogen, or, R36 and R38 together form a 4-7 membered heterocycle including the N and the Cα carbon, as defined for A above; and

R40 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group

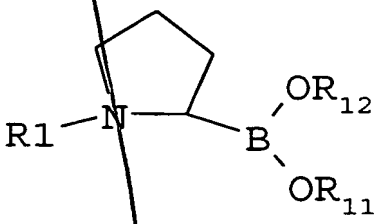
20. 21. The method of claim 16, wherein R2 is absent, or represents a small hydrophobic group.

21. 22. The method of claim 16, wherein R3 is a hydrogen, or a small hydrophobic group.

22. 23. The method of claim 16, wherein R5 is a hydrogen, or a halogentated lower alkyl.

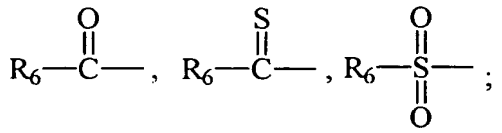
23. 24. The method of claim 16, wherein X1 is a fluorine, and X2 and X3, if halogens, are fluorine.

24. 25. The method of claim 16 ,wherein the inhibitor is represented by the general formula:



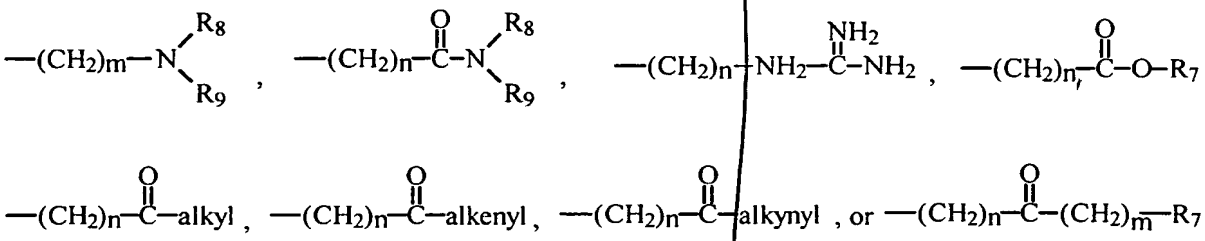
wherein

$R_1$ represents a C-terminally linked amino acid residue or amino acid analog, or a

terminally linked peptide or peptide analog, or  ;

C-

$R_6$ represents hydrogen, a halogen, a alkyl, a alkenyl, a alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



$R_7$ represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

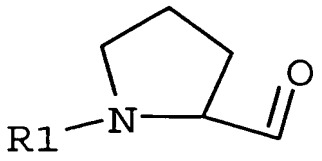
$R_8$ and $R_9$ each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, $-C(=O)-(CH_2)_m-R_7$,

or $R_8$ and $R_9$ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

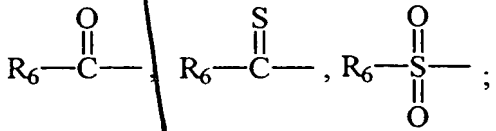
$R_{11}$ and $R_{12}$ each independently represent hydrogen, a alkyl, or a pharmaceutically acceptable salt, or $R_{11}$ and $R_{12}$ taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

25. The method of claim 16 ,wherein the inhibitor is represented by the general formula

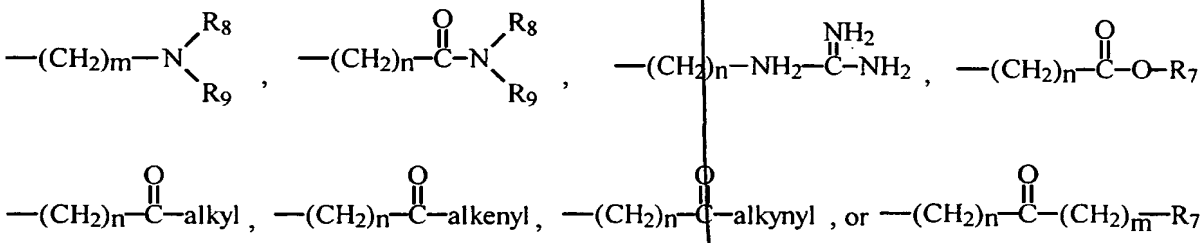


wherein

$R_1$ represents a C-terminally linked amino acid residue or amino acid analog, or a terminally linked peptide or peptide analog, or  ;

C-

$R_6$ represents hydrogen, a halogen, a alkyl, a alkenyl, a alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



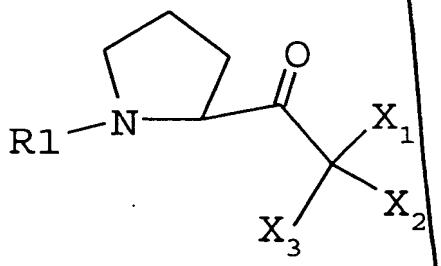
$R_7$ represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

$R_8$ and $R_9$ each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, $-C(=O)-(CH_2)_m-R_7$,

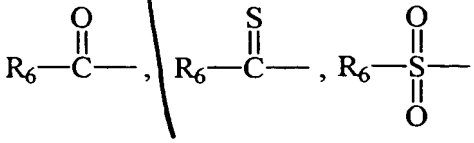
or $R_8$ and $R_9$ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure; and

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

27. The method of claim 16 ,wherein the inhibitor is represented by the general formula:

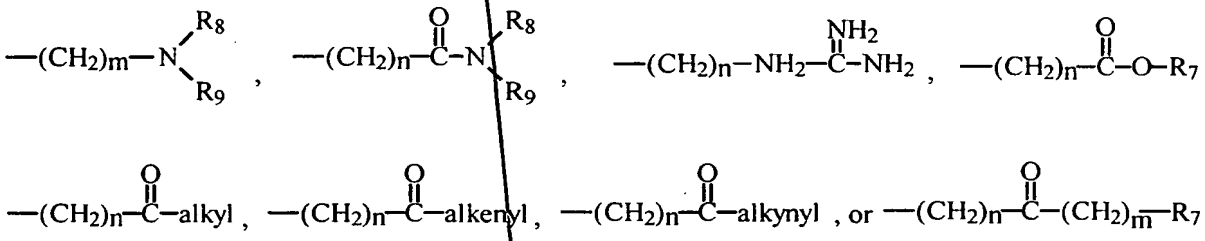


wherein

$R_1$ represents a C-terminally linked amino acid residue or amino acid analog, or a terminally linked peptide or peptide analog, or  ;

C-

$R_6$ represents hydrogen, a halogen, a alkyl, a alkenyl, a alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



$R_7$ represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

$R_8$ and $R_9$ each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, $-C(=O)-(CH_2)_m-R_7$,

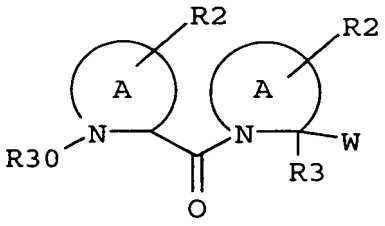
or $R_8$ and $R_9$ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

$X_1$, $X_2$ and $X_3$ each represent a hydrogen or a halogen; and

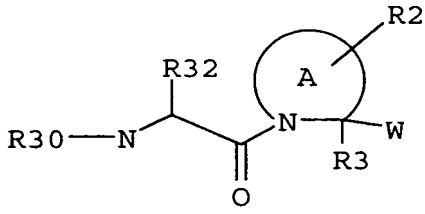
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

27

28. The method of claim 16 ,wherein the inhibitor is represented by the general formula:



or

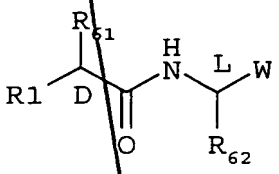


wherein

R32 is a small hydrophobic group; and

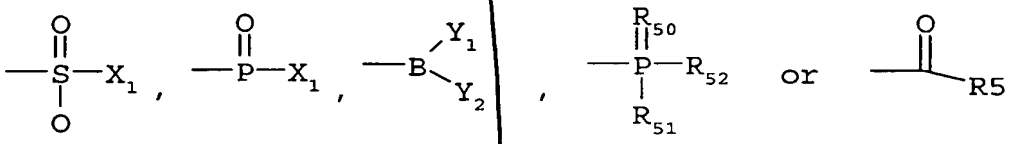
R30 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

~~28~~ ~~29~~. The method of claim 16 ,wherein the inhibitor is represented by the general formula:

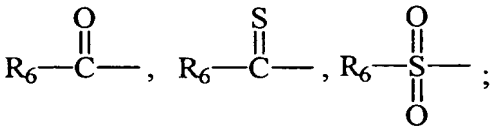


wherein

W represents a functional group which reacts with an active site residue of the targeted protease, as for example, -CN, -CH=NR$_5$,



R$_1$ represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



R$_3$ represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -(CH$_2$)$_m$-R$_7$, -(CH$_2$)$_m$-OH, -(CH$_2$)$_m$-O-lower alkyl, -(CH$_2$)$_m$-O-lower alkenyl, -(CH$_2$)$_n$-O-(CH$_2$)$_m$-R$_7$, -(CH$_2$)$_m$-SH, -(CH$_2$)$_m$-S-lower alkyl, -(CH$_2$)$_m$-S-lower alkenyl, -(CH$_2$)$_n$-S-(CH$_2$)$_m$-R$_7$;

R$_5$ represents H, an alkyl, an alkenyl, an alkynyl, -C(X$_1$)(X$_2$)X$_3$, -(CH$_2$)m-R$_7$, -(CH$_2$)n-OH, -(CH$_2$)n-O-alkyl, -(CH$_2$)n-O-alkenyl, -(CH$_2$)n-O-alkynyl, -(CH$_2$)n-O-(CH$_2$)m-R$_7$, -(CH$_2$)n-SH, -(CH$_2$)n-S-alkyl, -(CH$_2$)n-S-alkenyl, -(CH$_2$)n-S-alkynyl, -(CH$_2$)n-S-(CH$_2$)m-R$_7$, -C(O)C(O)NH$_2$, -C(O)C(O)OR'$_7$;

R$_6$ represents hydrogen, a halogen, a alkyl, a alkenyl, a alkynyl, an aryl, -(CH$_2$)$_m$-R$_7$, -(CH$_2$)$_m$-OH, -(CH$_2$)$_m$-O-alkyl, -(CH$_2$)$_m$-O-alkenyl, -(CH$_2$)$_m$-O-alkynyl, -(CH$_2$)$_m$-O-(CH$_2$)$_m$-R$_7$, -(CH$_2$)$_m$-SH, -(CH$_2$)$_m$-S-alkyl, -(CH$_2$)$_m$-S-alkenyl, -(CH$_2$)$_m$-S-alkynyl, -(CH$_2$)$_m$-S-(CH$_2$)$_m$-R$_7$,

R$_7$ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

$R'_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

$R_{61}$ and $R_{62}$, indepedently, represent small hydrophobic groups;

$Y_1$ and $Y_2$ can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where $Y_1$ and $Y_2$ are connected via a ring having from 5 to 8 atoms in the ring structure (such as pinacol or the like),

$R_{50}$ represents O or S;

$R_{51}$ represents $N_3$, $SH_2$, $NH_2$, $NO_2$ or $OR'_7$;

$R_{52}$ represents hydrogen, a lower alkyl, an amine, $OR'_7$, or a pharmaceutically acceptable salt, or $R_{51}$ and $R_{52}$ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure

$X_1$ represents a halogen;

$X_2$ and $X_3$ each represent a hydrogen or a halogen

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

29

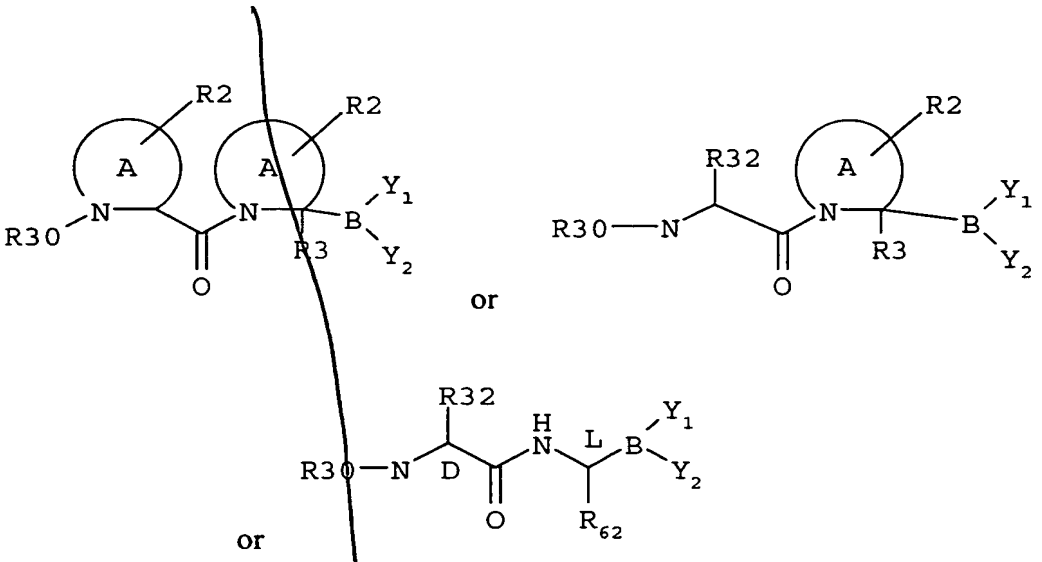
~~30~~. A method for modifiying, in an animal, metabolism of peptide hormone, comprising administering to the animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) in an amount sufficient to increase the plasma half-life of a peptide hormone, which peptide hormone is selected from the group consisting of glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

30

~~31~~. A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including boronyl peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

31

~~32~~. The method of claim ~~31~~ 30, wherien the boronyl peptidomimetic is represented in the general formula:



or



or

wherein

each A independently represents a 4-8 membered heterocycle including the N and the Cα carbon;

$R_2$ is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_7$;

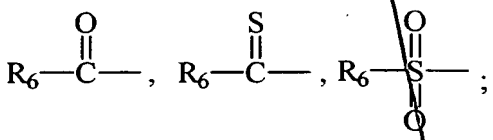
$R_3$ represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_7$;

$R_5$ represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, -(CH2)m-R7, -(CH2)n-OH, -(CH2)n-O-alkyl, -(CH2)n-O-alkenyl, -(CH2)n-O-alkynyl, -(CH2)n-O-(CH2)m-R7, -(CH2)n-SH, -(CH2)n-S-alkyl, -(CH2)n-S-alkenyl, -(CH2)n-S-alkynyl, -(CH2)n-S-(CH2)m-R7, $-C(O)C(O)NH_2$, -C(O)C(O)OR'7,

$R_6$ represents hydrogen, a halogen, a alkyl, a alkenyl, a alkynyl, an aryl, -$(CH_2)_m$-$R_7$, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-$R_7$, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-$R_7$,

$R_7$ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

$R_{30}$ represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



;

$R_{32}$ and $R_{61}$, indepedently, represent small hydrophobic groups, preferably lower alkyls, and more preferably methyl;

$Y_1$ and $Y_2$ can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where $Y_1$ and $Y_2$ are connected via a ring having from 5 to 8 atoms in the ring structure (such as pinacol or the like),

m is zero or an integer in the range of 1 to 8, and n is an integer in the range of 1 to 8.

R.126 32 ~~33~~. The method of claim 31 ~~32~~, wherein administering the boronyl peptidomimetic reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia.

R.126 33 ~~34~~. The method of claim 31 ~~32~~, wherein the boronyl peptidomimetic has an EC50 for modification of glucose metabolism which is at least one order of magnitude less than its EC50 for immunosuppression.

R.126 34 ~~35~~. The method of claim 31 ~~32~~, wherein the boronyl peptidomimetic has an EC50 for inhibition of glucose tolerance in the nanomolar or less range

R.126 35 ~~36~~. The method of claim 31 ~~32~~, wherein the boronyl peptidomimetic has an EC50 for immunosuppression in the μM or greater range.

R1176 36 37. The method of claim 31 32, wherein the boronyl peptidomimetic is orally active.

R126 37 38. A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including boronyl inhibitor of peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.